In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: March 14, 2018

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ERIN QUACKENBUSH-BAKER, *	
*	No. 14-1000V
Petitioner, *	
v. *	Special Master Gowen
*	
SECRETARY OF HEALTH *	Entitlement; Off-Table Injury;
AND HUMAN SERVICES, *	Significant Aggravation;
*	Influenza ("Flu") Vaccination;
Respondent. *	Multiple Sclerosis.
* * * * * * * * * * * * * * * * * * * *	

Curtis R. Webb, Twin Falls, ID, for petitioner.
Christine M. Becer, United States Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On October 16, 2014, Erin Quackenbush-Baker ("petitioner") filed a claim for compensation pursuant to the National Vaccine Injury Compensation Program.[2] Petitioner alleges that as a result of receiving a trivalent influenza ("flu") vaccination on November 20, 2013, she experienced a significant aggravation of a pre-existing but asymptomatic multiple sclerosis ("MS"). Based on a full review of all of the evidence and testimony presented, I find that petitioner has established that she is entitled to compensation.

I. Procedural History

Petitioner initiated her claim on October 16, 2014. Petition. Following an initial status conference, petitioner confirmed that all relevant records had been filed. Respondent completed an initial review and elected to litigate the case. Petitioner filed five reports from neurologist Dr.

[1] Pursuant to the E-Government Act of 2002, see 44 U.S.C. § 3501 note (2012), **because this decision contains a reasoned explanation for the action in this case, I intend to post it on the website of the United States Court of Federal Claims.** The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." Id. **If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website without any changes.** Id.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-1 to 34 (2012) ("Vaccine Act" or "the Act"). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

Lawrence Steinman, M.D.[3] Petitioner's ("Pet.") Exhibits ("Exs.") 9, 11, 27, 30, 46. Respondent filed a Rule 4(c) Report recommending against compensation, as well as two reports from neurologist Dr. Thomas Leist, M.D. Respondent's ("Resp.") Exs. A, G.[4]

On January 7, 2016, the undersigned scheduled an entitlement hearing for February 2-3, 2017. As the case moved towards a hearing, the parties also explored the possibility of settlement. Petitioner obtained a neuropsychological evaluation and both parties retained life care planners to assess her needs. They exchanged offers but were ultimately unable to settle the case. On October 26, 2016, I awarded interim attorneys' fees and costs on petitioner's motion.

After the parties filed respective prehearing briefs and a joint prehearing submission, an entitlement hearing was held on February 2, 2017. Petitioner, Dr. Steinman, and Dr. Leist testified. The transcript was filed on February 23, 2017. Petitioner filed her post-hearing brief on April 28, 2017, and respondent filed his post-hearing brief on May 30, 2017. On June 9, 2017, petitioner filed a reply. This matter is now ripe for adjudication.

II. Standards for Adjudication[5]

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344). To receive compensation from the Program, a petitioner must prove either: (1) that she suffered a "Table" injury - i.e., an injury with onset within a particular period of time, corresponding to a particular vaccine listed on the Vaccine Injury Table – which creates a presumption of entitlement; or (2) an "off-Table" injury, which petitioner must establish was actually caused or significantly aggravated by the vaccine she received. W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1356-57 (Fed. Cir. 2013); Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Whether alleging a Table or an off-Table claim, a petitioner bears a "preponderance of the evidence" burden of proof. § 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence

[3] Dr. Steinman's curriculum vitae was filed as Pet. Ex. 10. The medical literature cited in his reports was filed as Pet. Exs. 12-26, 34, 40-44, 47-57, 60-62, 67.

[4] Dr. Leist's curriculum vitae was filed as Resp. Ex. B. The medical literature cited in his reports was filed as Resp. Exs. C-F.

[5] Decisions of special masters and the U.S. Court of Federal Claims (some of which are referenced in this ruling) constitute persuasive but not binding authority. Hanlon v. Sec'y of Health & Human Servs., 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. Guillory v. Sec'y of Health & Human Servs., 59 Fed. Cl. 121, 124 (2003), aff'd 104 F. App'x 712 (Fed. Cir. 2004); see also Spooner v. Sec'y of Health & Human Servs., No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly, 592 F.3d at 1322 n.2; see also Snowbank Enter. v. United States, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 13(a)(1).

Here, petitioner is claiming an off-Table injury. Moreover, petitioner does not allege that she did not have MS before she received the flu vaccine. Rather, she alleges that she previously had MS that was asymptomatic at the time of the flu vaccine and that the vaccine significantly aggravated that condition. As stated above, petitioner bears the burden of proof with this claim.

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4).

In Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009), the United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

The Federal Circuit endorsed this test in W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013).

The first three Loving prongs were first formulated as a test for Table significant aggravation claims. Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099 (Fed. Cir. 1996). In Whitecotton, the Federal Circuit cited legislative history regarding what constitutes a significant aggravation: "This provision does not include compensation for conditions which might legitimately be described as pre-existing (e.g., a child with monthly seizures who, after vaccination, has seizures every three and a half weeks), but is meant to encompass serious deterioration (e.g., a child with monthly seizures who, after vaccination, has seizures on a daily basis)." Id. at 1102-03 (citing H.R. Rep. 908, 99th Cong.2d Sess. 1, reprinted in 1968 USCCAN 6287, 6356). With regard to the legal standard for these claims, the Federal Circuit

acknowledged the difficulty of predicting the course of a preexisting condition if the vaccine were not administered. They held that a petitioner alleging significant aggravation of a Table injury was not required "to prove, as part of her *prima facie* case, that petitioner's significant aggravation was not caused by a preexisting injury." Id. at 1106. Instead, "once a petitioner has made a *prima facie* case, the government may still prevail if it can show, to a preponderance of the evidence, that the pre-existing condition was in fact, the cause of the individual's post-vaccination significant aggravation." Id. at 1107 and 1107, n. 13.

In W.C., the Federal Circuit held that the same inquiry applies when evaluating whether a petitioner suffered a significant aggravation of an off-Table injury. W.C., 704 F.3d at 1356-57. However, petitioner has the burden of establishing each prong, including that her current condition constitutes a significant aggravation. Id. The Federal Circuit did not elaborate on the petitioner's burden, i.e., whether she must establish that her condition would not have progressed to the same extent in the absence of the vaccine *or* under which Loving prong that burden would fit. Prior to the Federal Circuit's issuance of W.C., then-Special Master Vowell suggested in the context of an off-Table significant aggravation claim:

> "Exactly who has the burden to demonstrate what the petitioner's condition would have been, but for the vaccine, remains somewhat amorphous. To meet the significant factor and but-for tests set forth in Shyface, 165 F.3d at 1352, the burden would appear to be petitioner's."

Hennessey v. Sec'y of Health & Human Servs., No. 01-190V, 2009 WL 1709053, at *58 (Fed. Cl. Spec. Mstr. May 29, 2009), motion for review denied, 91 Fed. Cl. 126 (2010); see also Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 731 (2011) (holding that a special master did not abuse his discretion upon finding that petitioner failed to present persuasive evidence that separated her alleged vaccine injuries from an expected course of her pre-existing condition).

Loving prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. Althen v. Sec'y of Health & Human Servs., 17 F.3d 374 (Fed. Cir. 1994). Under the fourth prong (Althen prong three), petitioners must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. Pafford, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." Id. at 549. This prong does not specifically require medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish Althen prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Id. at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. Contreras v. Sec'y

of Health & Human Servs., 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility . . . in many cases may be enough to satisfy Althen prong one" (emphasis in original)), vacated on other grounds, No. 2015-5097 (Fed. Cir. Jan. 3, 2017). But this does not negate or reduce a petitioner's ultimate burden to establish his or her overall entitlement to damages by preponderant evidence. W.C., 704 F.3d at 1356.

Loving prong five (Althen prong two) requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. Althen, 418 F.3d at 1278; Andreu, 569 F.3d at 1375-77; Capizzano, 440 F.3d at 1326; Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting Althen, 418 F.3d at 1280). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. Hibbard v. Sec'y of Health & Human Servs., 100 Fed. Cl. 742, 749 (2011) (holding that it was not arbitrary or capricious for a special master to weigh competing treating physicians' conclusions against each other), aff'd, 698 F.3d 1355 (Fed. Cir. 2012); Caves v. Sec'y of Dept. of Health & Human Servs., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), mot. for review den'd, 100 Fed. Cl. 344, 356 (2011), aff'd without opinion, 475 Fed. App'x 765 (Fed. Cir. 2012).

As noted above, there is some ambiguity as to whether a petitioner bringing a significant aggravation claim must establish that absent the vaccine, her pre-existing condition would not have progressed the way it did. If that is petitioner's burden, it is ambiguous if whether that falls under Loving prong three (establishing the significant aggravation itself) or Loving prong five (establishing a logical sequence of cause and effect). In Hennessey, the special master suggested that the natural course of the condition should be considered under Loving prong five (Althen prong two), to pass the significant factor and but-for tests set forth in Shyface, 165 F.3d at 1352. Hennessey, 2009 WL 1709053, at *58; see also H.L. v. Sec'y of Health & Human Servs., No. 10-0197V, 2016 WL 3751848, at *20 (Fed. Cl. Spec. Mstr. March 17, 2016) (finding that petitioner had established a significant aggravation, taking that term to mean "a significant worsening, without any implication as to the cause of the worsening"). However, a petitioner is not required to eliminate all possible alternative causes of the injury. See Walter v. Sec'y of Health & Human Servs., 485 F.3d 1146, 1150 (Fed. Cir. 2007) ("the Vaccine Act does not require the petitioner to bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a *prima facie* case"). This standard permits the use of "circumstantial evidence" and accomplishes Congress's goal that "close calls regarding causation are resolved in favor of injured claimants." Althen, 165 F.3d at 1280.

Loving prong six (Althen prong three) requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." Id. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." De Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (Althen prong one's requirement). Id. at 1352; Shapiro v. Sec'y of Health & Human Servs., 101 Fed. Cl. 532, 542 (2011), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 2013 WL 1896173 (Fed. Cir. 2013); Koehn v. Sec'y of Health & Human Servs., No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), mot. for review den'd (Fed. Cl. Dec. 3, 2013), aff'd, 773 F.3d 1239 (Fed. Cir. 2014).

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any Althen prong. Grant, 956 F.2d at 1149; Andreu, 569 F.3d at 1380. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met their burden of proof.

Once a petitioner fulfills the six Loving prongs, the burden of persuasion shifts to respondent to show that the alleged injury was caused by a factor unrelated to the vaccination. Knudsen, 35 F.3d 543 at 548; § 13(a)(1)(B). Respondent has the burden of demonstrating that "a factor unrelated to the vaccination is the more likely or principal cause of the injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was 'principally responsible' for the injury." Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363, 1369 (Fed. Cir. 2013). Section 13(a)(2) specifies that factors unrelated "[do]not include any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." Close calls regarding causation must be resolved in favor of the petitioner. Althen, 418 F.3d at 1280; Knudsen, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

III. Summary of Relevant Facts[6]

1. Petitioner's Medical History Prior to Vaccination on November 20, 2013

Petitioner's medical history was significant for three caesarean sections and a past history of anxiety which had resolved. Pet. Ex. 2 at 3; Pet. Ex. 5 at 37. She had no family history of neurologic or autoimmune diseases. Pet. Ex. 2 at 3; Pet. Ex. 5 at 37. Petitioner received a flu vaccine on September 25, 2009. Pet. Ex. 39 at 2. She received another flu vaccine on October

[6] I have considered the record as a whole in reaching my decision. This summary contains a review of the facts most relevant to disposition of this case.

24, 2011. Pet. Ex. 3 at 9. She complained of upper respiratory symptoms in December 2011, May 2012, and June 2012. Pet. Ex. 2 at 10-19.

On June 29, 2012, petitioner went to her primary care provider with a one-week history of "sharp and burning" pain in her left shoulder, radiating to the arm, wrist, and hand. Her hand was also numb. A physical exam of the left shoulder and hand found "normal skin, soft tissue and bony appearance without gross edema or evidence of acute injury." The left shoulder had a full range of motion. Palpation elicited pain in the lateral deltoid. Petitioner was told to rest, ice, compress, and elevate the shoulder (RICE) and to limit her range of motion. She was told to wear a brace on her hand at night. She was prescribed Medrol (methylprednisone - a corticosteroid) and told to call if she developed new or worsening symptoms. Pet. Ex. 2 at 20-22. The parties stipulate that petitioner "received no treatment for the symptoms, and they went away within a few days of the June 29, 2012, doctor's appointment." Joint Prehearing Submission, ¶ 3. On August 14, 2012, petitioner returned to the primary care provider for a routine periodic health screening. The records do not mention shoulder or wrist symptoms. Pet. Ex. 2 at 23-25.

On August 22, 2013, she went to her family doctor with a one-week history of episodes of "diffuse… severe… burning… abdominal pain radiat[ing] to the left flank and right flank." The doctor did not believe it was an obstruction, urinary tract infection, or renal lithiasis. He was suspicious of gastritis, some other peptic disease, or perhaps gallbladder disease. He ordered an H2 blocker and a proton pump inhibitor to start. Pet. Ex. 3 at 4-5.

On October 14, 2013, petitioner went to the emergency room for persistent pain in her right upper jaw and her neck since undergoing dental work. She did not have a fever. No external evidence of infection or surgical complications was found. Petitioner was told to follow up with her dentist. Pet. Ex. 5 at 4-7.

2. November 20, 2013 Flu Vaccination and Subsequent Medical History

On November 20, 2013, "petitioner was healthy (she had no symptoms of multiple sclerosis at that time)." Joint Prehearing Submission at 2. She had just received her real estate license and was about to start a job. She was the principal caregiver for three children: a 6-year-old daughter, a 4-year-old son, and a 23-month-old son. Joint Prehearing Submission at 2. Petitioner and the children went to their primary care provider for routine check-ups. It was suggested that petitioner and her children all get vaccinated for the flu. The holidays were approaching and they would be hosting family from out of town; the children were young; and they shared their home with petitioner's grandmother, who had cancer and therefore a weakened immune system. Petitioner recalled being told not to get vaccinated if anyone was sick. She agreed to the vaccinations because "everyone was feeling so good." Upon receiving the flu vaccine, she had no symptoms of infection – no fever, no cough. Neither did any of the children have fevers or coughs before being vaccinated. Her 6-year-old daughter received FluMist and MMR vaccines; her 4-year-old son received FluMist, polio, tetanus, and pertussis; and her 23-month-old son received FluMist. Affidavit at 1-2, Tr. 69-71. Petitioner received a trivalent influenza vaccination (Fluvirin 2013-2014). Pet. Ex. 3 at 11. This record of the vaccine

administration is dated November 20, 2013 at 12:30 p.m. There are no notes of petitioner's condition or what was discussed.

The next day, Thursday, November 21, 2013, petitioner and her children "were not feeling [their] best, but were fine to go about [their] day." On Friday, November 22, 2013, at approximately 5:30 a.m., petitioner awoke and noticed that her feet felt "asleep" (numb). They remained numb and "tingly" throughout the day. All three children had fevers: the 6-year-old daughter was sent home with a temperature of 102; the 4-year-old son had a temperature of 102 and a cough; and the 23-month-old son had a temperature of 103. Petitioner testified that their doctor thought it was a reaction to their vaccinations. The children were given Tylenol and Motrin. However, petitioner did not develop a fever. Affidavit at 2-3; Tr. 70-71.

On Saturday, November 23, 2013, at about 4:00 a.m., petitioner woke because she was numb from the hips down. Affidavit at 2; Tr. 72. She checked on the children and discovered that the 6-year-old daughter and 4-year-old son's fevers remained at 102 and the 23-month-old son's fever had risen to 104. Affidavit at 3. Petitioner went with one or more of the children to the primary care provider. Affidavit at 3 (23-month old-son); Tr. 107 (6-year-old daughter). Petitioner was examined at approximately 10:30 a.m. She reported a 2-day history of "pins and needles in legs." The record reads: "Feet with numbness and tingling yesterday. Has now spread up entire legs into genital area and lower abdomen. No leg weakness, no bowel or bladder incontinence, no back pain. No fevers . . . . Recently had flu shot." Petitioner had a normal temperature as well as normal breath effort and sounds. The primary care provider's assessment was "paresthesia of bilateral legs." Because the paresthesia was not associated with weakness and loss of reflexes, the primary care provider doubted Guillain-Barré syndrome. Because the paresthesia was rapidly progressing and it involved the lower torso, she suspected the presence of a spinal cord lesion. She ordered a lumbar spine MRI. Pet. Ex. 3 at 13-14.

That afternoon, petitioner (accompanied by her grandmother) traveled about 75 miles to Twin Falls, Idaho for the MRI. Tr. 73. It had no abnormal findings in the lumbar spine area. Pet. Ex. 3 at 41-42; Pet. Ex. 4 at 1-3. The records indicate "no recent infection." Pet. Ex. 4 at 2. Petitioner also underwent a chest X-ray, which exhibited clear lungs and no acute abnormality. Pet. Ex. 3 at 43; Pet. Ex. 5 at 161. Petitioner was told to continue monitoring the numbness, because if it rose higher than her waist, it could impair her breathing. It did progress. By that evening, petitioner was numb from her feet to just below her rib cage. Affidavit at 3; Tr. 74.

That night at approximately 5:42 p.m., petitioner presented to the emergency department at the Wood River Medical Center ("WRMC") in Ketchum, Idaho. She was admitted later that night. Pet. Ex. 5 at 14. An intake or triage record made at approximately 10:14 p.m. states that petitioner "has not had a fever recently but does endorse recent runny nose. She does endorse having had her flu shot 5 days ago. She also endorses that all 3 of her kids have had flulike symptoms over the last week." Pet. Ex. 5 at 21.[7] Her temperature was normal. A physical exam noted that her neck was "supple with good range of motion, flexion, extension and rotation.

[7] On cross-examination, petitioner denied any memory of this runny nose. She did remember her children having temperatures, but only after getting their flu shots. She did not remember the length of time between the children's vaccinations and when their symptoms began. Tr. 105-06.

Negative Lhermitte sign[8] for neck flexion and extension." Pet. Ex. 5 at 17. Laboratory testing of petitioner's blood drawn on November 23, 2013, showed normal white blood cell and ESR values, but high lymphocytes (100, compared to range of 0-80). Pet. Ex. 5 at 26, 29. Laboratory testing of petitioner's cerebrospinal fluid ("CSF") drawn on November 23, 2013, at 9:25 p.m., showed an IgG index of 0.71 (above the reference range of 0.28-0.66); 6 CSF oligoclonal bands (above the reference range of 0-1 bands); positive MS oligoclonal bands (normally negative); myelin basic protein at 21.90 ng/ml (above the reference range of 0.00-5.50 ng/ml). Pet. Ex. 5 at 192. The final result of the CSF culture and gram smear of the CSF was "no organisms seen; few WBCs seen; and culture: no growth 1 week." Pet. Ex. 3 at 66.

A progress note from Sunday, November 24, 2013, at 1:28 a.m., states that petitioner "denied any fevers, chills, back pain, neck pain, headache but states she did have a headache the day of the flu shot." Petitioner denied "runny nose, sore throat [or…] a cough." Pet. Ex. 5 at 38. She "[did] have one child home with a fairly high temperature but otherwise has not had any preceding illness or known exposures." Pet. Ex. 5 at 9.

Also on November 24, 2013, a neurologist, Dr. Karin Lindholm, recorded that petitioner was a "36-year-old female with new onset dysesthesias [which…] started approximately 36 hours post-flu vaccination but was exposed to two children at home with high fevers." Dr. Lindholm recorded that petitioner's elevated white blood count was consistent with "early Guillain-Barre but also other post-infectious or inflammatory autoimmune processes affecting nervous system [and…] acute CNS demyelinating processes." Pet. Ex. 5 at 18.

Petitioner was discharged from the hospital on Sunday, November 24, 2013, with instructions to return for a brain MRI. Pet. Ex. 5 at 14. On Monday, November 25, 2013, the brain MRI revealed: "8 foci of T2 hyper-intensity in the cerebral white matter. 3 of these are in the white matter of the temporal lobes. At least 2 of these foci are radiating away from the lateral ventricles, with a Dawson's finger appearance. There is one enhancing lesion in the subcortical white matter of the right parietal lobe that also demonstrates diffusion restriction. No lesions seen within the brain stem or posterior fossa. The largest lesion measures up to 10 mm in length." The "foci of T2 hyperintensity in the cerebral white matter [were] somewhat non-specific but [were] concerning for demyelinating lesions given their appearance and location. One enhancing lesion in the right parietal lobe [was] consistent with a site of active demyelination." Pet. Ex. 5 at 162.

On Monday, November 25, 2013, petitioner returned to Dr. Lindholm at St. Luke's Neurology Clinic in Hailey, Idaho. Dr. Lindholm recorded that the numbness had reached the "mid-trunk level." Pet. Ex. 3 at 15; Pet. Ex. 6 at 1-4. Dr. Lindholm also observed "abnormal CSF studies with mild elevation in the WBC count (19 WBC) with 100% lymphocytes." Pet. Ex. 3 at 17. "These findings are suggestive of an acute inflammatory or demyelinating disease process currently affecting the central nervous system without evidence at this time for peripheral nerve involvement. It is, however, early in the disease process and nerve conduction studies may need to be repeated in one to 2 weeks to evaluate for acute inflammatory

[8] Lhermitte's sign is "the development of sudden, transient, electric-like shocks spreading down the body when the patient flexes the head forward; seen mainly in MS but also in compression and other disorders of the cervical cord." Dorland's Illustrated Medical Dictionary ("Dorland's") (32d ed. 2012) at 1738.

polyradiculoneuropathy which may not be evidence[d] on nerve conduction studies for up to one to 2 weeks." Dr. Lindholm ordered a thoracic spine MRI, followed by the administration of Solumedrol (a corticosteroid). Pet. Ex. 3 at 17.

The thoracic spine MRI, performed the next day, visualized "from the level of the bottom of C4 through the conus which is at the level of L1." It showed "a single T2 hyperintense lesion within the central slightly posterior cord centered at the level of C7 and measuring 4 x 4 mm transverse and 6 mm craniocaudal" that enhanced with contrast. The enhancing T2 lesion was "concerning for a demyelinating lesion," given the findings of the recent brain MRI. Pet. Ex. 5 at 164-65.

On November 29, 2013, at approximately 9:15 p.m., petitioner returned to the emergency department at WRMC. She reported that the numbness had risen to "the area between the nipples and the clavicles," she was "having trouble walking," and "her legs [were] getting heavier." The attending physician examined petitioner, then contacted Dr. Lindholm, who felt it was "too early to expect results from the Solumedrol." Petitioner was directed to go home and contact Dr. Lindholm the next day. She left the hospital at approximately 11:50 p.m. Pet. Ex. 5 at 53-67; see also Joint Pre-Hearing Submission at 4.

On November 30, 2013, petitioner's grandmother drove her to the University of Utah Medical Center in Salt Lake City for more specialized care for her progressively worsening condition. She was admitted to the university hospital on December 1, 2013, at approximately 3:00 a.m., where she remained until December 12, 2013.[9] Pet. Ex. 7 at 4, 15-27. On December 1, 2013, the attending physician, Dr. John Greenlee, recorded:

> "Neurologic examination significant for bilateral lower extremity hyperesthesia and hyperreflexia, with mild left-sided hemiparesis; these findings would best singly localize to an upper motor cord lesion. However, imaging confirms both enhancing and non-enhancing lesions in the brain and lower cervical cord. Given her history, physical exam, and imaging, differential diagnosis includes MS, NMO [neuromyelitis optica], transverse myelitis, ADEM [acute disseminated encephalomyelitis], Sjogren's syndrome, or possibly VZV infection. ADEM often occurs following vaccination, which would fit the patient's history. She does not appear to be acutely infected, so a viral illness is less likely." Dr. Greenlee also wrote: "The patient's course and MRI findings are more suggestive of MS, however she has absolutely no prior history of signs or symptoms to suggest MS, and the temporal association with her influenza vaccination is worrisome. ADEM is not ruled out by her studies to date, although the time interval between immunization and onset is unusually short."

[9] Petitioner testified that while she was at the University of Utah Medical Center, her 6-year-old daughter continued to experience a fever persisted and also developed a rash. The daughter "did go to the emergency room and may have stayed the night, because she developed an illness, which they associated with just reacting to the shot. They said it's typical and not to be concerned, but it happened when I wasn't with her." Tr. 70-71.

Later, on December 4, 2013, Dr. Greenlee wrote: "The great likelihood is that this patient does not have ADEM but rather may have induced an exacerbation of her MS with immunization, although the two events could also have been coincidence." Pet. Ex. 7 at 45-46.

A cervical spine MRI was performed on December 1, 2013. A neurology resident, Dr. Gurjeet Singh, wrote: "T2 hyperintense focal short segment cervical cord lesion at C7 with unchanged enhancement along its inferior portion. Small non-enhancing lesion in the left posterolateral cord at the C3-C4 level. Given the intracranial findings on the outside MRI and the features of the cord lesions, a demyelinating process, such as MS, is favored. ADEM is an additional consideration, although thought to be less likely given the appearance and morphology of the supratentorial and cervical cord lesions." In the history of present illness, Dr. Singh wrote that "on 11/30/13[10] she had a flu vaccine… after the vaccine, she immediately felt a weird sensation in her chest." Dr. Singh also wrote: "Given recent vaccination and lack of prior history consistent with MS, ADEM was differential, but she had no clinical feature of ADEM." Pet. Ex. 7 at 16-18. Dr. Singh later commented that petitioner's "negative antibodies for aquaporin 4, present oligoclonal bands, elevated CSF IgG and IgG synthesis rates" were supportive of MS. Pet. Ex. 7 at 53. He also stated that petitioner's "imaging is most consistent with MS, though she has no prior symptoms to account for her other non-enhancing lesions." Pet. Ex. 7 at 64.

On December 11, 2013, Dr. Jennifer Juhl Majersik, an assistant professor and treating neurologist, wrote that ADEM was "not still on the differential" and diagnosed petitioner with MS. Pet. Ex. 7 at 89. After receiving five rounds of plasmapheresis and seeing some improvement, petitioner was discharged on December 12, 2013. Pet. Ex. 7 at 18-19. She was still numb from her collarbone to her toes. Affidavit at 5.

Beginning on December 14, 2013, petitioner experienced difficulty swallowing. She felt that solid food "hung up in mid-esophagus," although she had no difficulty drinking water. Pet. Ex. 5 at 63-64. She went to the emergency room, where she was evaluated, discharged, and directed to take an antihistamine and to drink thick liquids. Pet. Ex. 5 at 63-67; see also Pet. Ex. 7 at 125-26 (University of Utah telephone call records from this period). An esophogram conducted on December 23, 2013, was normal. Pet. Ex. 5 at 166.

Petitioner was referred to Dr. John Steffens, a neurologist with expertise in MS located in Twin Falls, Idaho. Petitioner first spoke to Dr. Steffens on the phone, then had her first appointment with him on December 31, 2013. He recorded that petitioner "had received a flu vaccine and felt immediately a weird sensation in her chest. Two days later, she began noticing paresthesias, pins and needles, in her feet."[11] The most significant issues were a "persistent Lhermitte's phenomena when she flexes her neck,[12] a sensory level of dysesthesias to about her

[10] This appears to be a typo, as the vaccine was actually administered on November 20, 2013. Pet. Ex. 3 at 11.

[11] When questioned about this record at the entitlement hearing, petitioner testified: "Well, the only thing I remember about a chest issue is I had my first flu vaccine ever in 2009, and I had that feeling with that one, a weird sensation in my chest and it felt weird for a few days . . . . But I had that in 2009, so I don't know if I was referring to that, maybe, or if I was referring to the current time." Tr. 107-08.

[12] Compare Pet. Ex. 5 at 17 (WRMC record from November 23, 2013, noting "negative Lhermitte sign for neck flexion and extension").

hips that seems to be getting "lighter" over time, and this persistent sense of any kind of stimulation causing worsening electrical buzzing sensation in her legs and hips." Dr. Steffens also noted "intact cranial functions except for a couple beats of nystagmus on lateral gaze to the left." Petitioner was noted to have weakness and memory loss. Dr. Steffens prescribed Copaxone and 10,000 units of Vitamin D daily for the next 3 months. Pet. Ex. 8 at 2-4.

On January 14, 2014, in the middle of the night, petitioner awoke with "significant," "excruciating" pain in her left shoulder, arm, chest, and back, for which she went to the emergency room. Pet. Ex. 5 at 73-74. Lab work found neutrophils at 33% (below the reference range of 40-76%); lymphocytes at 56% (above the reference range of 24-44%); 17.8 MMOL/L CO2 (below the reference range of 22-32 MMOL/ L); and glucost at 102 MG/ DL (above the reference range of 60-100 MG/ DL). Pet. Ex. 3 at 7; Pet. Ex. 5 at 80. The attending physician "suspect[ed] this [was] MS related—dystonic issue." The attending physician spoke to Dr. Steffens, who "recommended against steroids[,] suggested Baclofen for spacticity[, and] recommend[ed] that [petitioner] continue her Copaxone injections." Dr. Steffens "felt that the lesion in [petitioner's] spine could be causing her symptoms." Pet. Ex. 5 at 84.

On January 17, 2014, petitioner had a follow-up with Dr. Steffens. She indicated that she had taken one Copaxone shot and then experienced symptoms such as chest tightness, lightheadedness, wooziness, dizziness, fear, anxiety, and swelling/ soreness at the injection site. Shortly after, she began getting recurrent dysthesias and discomfort of her right side and her leg became numb. She subsequently went to the emergency room (see preceding paragraph). Dr. Steffens observed petitioner take a Copaxone shot, after which she developed hives/ redness and hyperventilation, as she had described happening previously. Dr. Steffens concluded this was not a Copaxone side effect, but, rather, anxiety. He did note new discomfort and numbness in her right leg and a worsened spastic and hemiparetic gait. Dr. Steffens increased her Baclofen, recommended continuing Copaxone, and said that what petitioner was experiencing "while not comfortable and not optimal, is part of the whole evolutionary process of her MS as she continues to work through the initial attack." Pet. Ex. 8 at 6-8.

Also in January 2014, petitioner developed a blind spot in the upper right quadrant of her vision. Affidavit at 6-7; Pet. Ex. 3 at 23-28; Pet. Ex. 8 at 3. On February 12, 2014, petitioner underwent a brain MRI with and without contrast. It observed: "Interval increase in size and number of T2 hyperintense lesions within the brain, consistent with progression of MS compared to 11/25/2013. There are multiple new enhancing lesions within the brain. There are 2 somewhat large new lesions, one in the left temporal lobe measuring up to 3.3 cm and another in the left periatrial and deep white matter measuring up to 1.5 cm." Therefore, there were a total of "15-20 lesions," of which seven were enhancing. Pet. Ex. 5 at 170.

During February and March 2014, petitioner developed weakness in her arms and legs and began to have difficulty with multitasking and memory. Affidavit at 7; Pet. Ex. 8 at 4, 7. Around this same time period, petitioner had sinusitis and or an upper respiratory infection, for which she was prescribed antibiotics. Pet. Ex. 3 at 33-37.

On March 3, 2014, petitioner returned to Dr. Steffens. Dr. Steffens discussed that petitioner's "MRI show[ed] new and enlarging lesions compared to her original series of MRIs." Dr. Steffens continued: "It is impossible to tell how many of these represent 'new disease activity' versus a 'coasting phenomenon' given the fact that MRI lesions do not appear immediately on MRIs at the time of the clinical manifestations." He also recommended waiting to see how her MS responded to the Copaxone because "the first 3 months after starting a therapy don't count." Pet. Ex. 8 at 12-14. On March 17, 2014, petitioner saw Dr. Steffens again. He did not record any change in her condition, but discussed managing her psychological response to her medical condition. Pet. Ex. 8 at 15-17. On April 4, 2014, MRIs of the thoracic and cervical spinal cord did not reveal significant change. Pet. Ex. 5 at 172.

On April 21, 2014, petitioner saw Dr. Steffens again. He noted: "Her course has been plagued by resurgence of her symptoms in January and February, for which she has had IV steroids. She has had multiple colds, upper respiratory infections, etc., and has been treated concomitantly, and recently for 'walking pneumonia' that was diagnosed in the emergency room at [WRMC]." He wrote that the brain MRI and an ophthalmology consult suggested that a brain lesion was the cause of petitioner's right-sided visual deficits. Dr. Steffens had scheduled this routine follow-up in recognition of petitioner's anxiety, but on examination, he was "pleased with her progress," opining: "We are starting to see the benefit of her Copaxone and she is starting to 'cool off' with her disease state." Pet. Ex. 31 at 2-4.

On April 30, 2014, petitioner went to the emergency room, reporting that for the "last few months," she had a sore throat, a "choking" sensation, and difficulty swallowing. The attending physician at WRMC ordered a soft tissue neck x-ray. Pet. Ex. 5 at 139-45. On May 14, 2014, while visiting California, petitioner sought treatment for tightness in her throat, which was diagnosed as laryngopharyngeal reflux disease. Pet. Ex. 35 at 2-4.

On June 14, 2014, petitioner experienced an episode of back spasms, difficulty breathing, and sensory symptoms in her hands and face for which she went to the WRMC emergency room. She was counseled for anxiety but there was no suspicion of significant MS exacerbation requiring new treatment, and she was sent home that night. Pet. Ex. 5 at 149-55.

On June 19, 2014, petitioner had a follow-up with Dr. Steffens. Dr. Steffens noted petitioner's multiple colds. Dr. Steffens reviewed certain "MRIs done in California which include no visible lesions on the [cervical] spine and [thoracic] spine, MRI of the brain reveals a couple of small enhancing lesions but actually a reduction in total number of enhancing lesions and reduction in size of existing lesions compared to previous scans. Both of these results are improved compared to their prior imaging." He prescribed an antidepressant and an increased intake of vitamin D. Pet. Ex. 31 at 5-7.

On July 22, 2014, petitioner sought a second opinion from Dr. Jonathan Carter, a neurologist at the Mayo Clinic in Arizona. Dr. Carter's impression was that petitioner was experiencing "worsening symptoms about every 2 weeks or so on average which then subside to baseline." Pet. Ex. 34 at 3-6. Dr. Carter ordered MRIs of the brain and cervical spine, which showed "significant improvement" and no new lesions. Pet. Ex. 34 at 7, 16-17. Neuropsychological testing was suggestive of "very mild cognitive inefficiency," which could be

attributed either to MS or petitioner's admitted sleep deprivation and anxiety. Pet. Ex. 34 at 7-8, 34-36.

On August 11, 2014, Dr. Steffens did a routine follow-up and noted slight improvement to petitioner's physical and mental state. Pet. Ex. 31 at 8-10. On September 27, 2014, petitioner went to the WRMC emergency room with a several-day history of numbness in her left hand and tingling on the bottom of both feet. She also complained of significant fatigue for the past few weeks. She would get up each morning to get her children to school. Then she would sleep during the day until it was time to pick them up. The attending physician recommended following-up with Dr. Steffens and resuming regular appointments with a therapist. Pet. Ex. 32 at 19-23. On October 7, 2014, petitioner returned to the emergency room after experiencing an immediate post-injection reaction to the Copaxone. Pet. Ex. 32 at 24-28.

In October 2014, December 2014, April 2015, and June 2015, Dr. Steffens assessed petitioner's condition to be stable and did not observe any new symptoms. Pet. Ex. 31 at 11-31. In late June 2015, petitioner and her family moved from Idaho to Arizona. Pet. Ex. 36 at 7.

On August 16, 2015, petitioner went to the emergency room at the Mayo Clinic, where she reported a 1.5-week-long history of "difficulty with her memory and thinking." Pet. Ex. 34 at 41-43. The attending physician did not identify any "hard focal neurologic deficits that would necessitate an emergent MRI," but ordered labs to rule out the possibility of an intercurrent infection that could be exacerbating her MS. Pet. Ex. 34 at 42.

On October 29, 2015, petitioner established care with Dr. Amy Borazanci at Barrow Neuroimmunology in Phoenix, AZ. Pet. Ex. 36 at 3-6. On February 8, 2016, petitioner returned to Dr. Borazanci for follow-up and complaints of difficulty multitasking, difficulty sleeping, and occasional impaired peripheral vision. Pet. Ex. 36 at 7-10. MRIs showed no changes in the spine or the brain between August 2015 and February 2016. Pet. Ex. 36 at 25-26, 38-39. On August 8, 2016, Dr. Borazanci again recorded that petitioner was experiencing difficulty multitasking, difficulty sleeping, and memory problems. Petitioner observed that she fared better in hot weather and worse in cold weather. She also felt socially awkward and easily stressed. Dr. Borazanci's recommendations included continuing 20mg of Copaxone each day and considering increasing the dosage to 40mg. Pet. Ex. 36 at 11-14.

The evidence submitted and the parties' joint prehearing submission indicate that in February - March 2014, petitioner developed weakness in her arms and legs. *See, e.g.*, Joint Prehearing Submission at ¶ 27. She also began to have difficulty with multitasking and memory. Id. Additionally, in early 2015, petitioner began reporting a change in her interpersonal skills (which she believes is a new lack of empathy) in her interactions with her husband and her children. Id. at ¶ 30. She continues to suffer varying degrees of numbness; fatigue; varying visual impairments; poor memory; difficulty concentrating; and a change in personality. Id. at ¶ 31. These symptoms have caused a great deal of anxiety, which has aggravated many of these symptoms. Id. at ¶ 32.

Because of these symptoms, petitioner is unable to care for her three young children without assistance. Her grandmother helps petitioner take care of herself, the children, and the

household. Tr. 84; 96-100. Petitioner stated that her grandmother is over 80 years old and has slow-moving leukemia. Tr. 87; Affidavit at 7.

Petitioner has also been unable to return to work selling real estate. Petitioner also testified that she had wanted, but was unable, to return to work. Affidavit at 7. She and her husband previously ran two restaurants; he was the chef, but she developed each concept, found the location, designed the restaurant, handled marketing, and greeted guests as they entered. Tr. 89-90; see also Tr. 85 (petitioner's testimony that she enjoyed the multitasking required to run the restaurants). Petitioner stated that they sold the restaurants after they had their third child in late 2011 and her husband secured a consulting job. Tr. 91. Petitioner stated that she began work as a real estate agent but went on leave. Tr. 87. She attempted to resume work in February 2014 and again in June 2014. However, she did not have enough energy, and she did not feel capable of speaking with clients or being responsible for legal documents. Tr. 87-89.

During the February 2017 entitlement hearing, petitioner testified that her travel and participation were exhausting and she would need a long time to recover. Tr. 92-93. She felt fatigued and stressed, and she was experiencing more spasticity, that is, her muscles were tight and unable to relax. Tr. 93-95.

Since approximately January 2014, petitioner has been taking Copaxone to treat her condition. Tr. 100. She self-administers an intradermal injection every day. She stated that the injection causes pain and inflammation, she has to rotate the site of injection, she has developed dents in her skin, and she is running out of places to inject. Tr. 101-02.

IV. Expert Qualifications

1. Petitioner's Expert, Dr. Lawrence Steinman, M.D.

Dr. Steinman is a board-certified neurologist. Pet. Ex. 10 at 2. He received a bachelor's degree from Dartmouth College and a medical degree from Harvard University, where he was also a NIH fellow. Id. After medical school, he completed an internship in surgery and residencies in pediatrics and pediatric and adult neurology at Stanford University. Id. He joined the faculty of Stanford University in 1980. Id. He is currently the chair of the University's Program on Immunology and the George A. Zimmerman Professor of Neurological Sciences, Neurology, Genetics, and Pediatrics. Id. He has authored a significant number of medical articles, holds numerous patents, and is admitted to several professional organizations. Dr. Steinman's research is focused on MS and related diseases, and approximately 2/3 of his patients have MS. Tr. 6. He is an invited member in neurology of the Institute of Medicine and has received the Charcot Prize for his lifetime contribution to MS research. I accepted Dr. Steinman as an expert in neurology, immunology, and MS. Tr. 8-9.

2. Respondent's Expert, Dr. Thomas Leist, M.D.

Dr. Leist is board-certified in neurology and psychiatry. Resp. Ex. B at 1; Tr. 111. After completing an undergraduate degree and a doctorate in biochemistry at the University of Zurich in Switzerland, he received a medical degree from the University of Miami. Exhibit B at 1. Dr.

Leist then had positions focusing on microbiology, immunology, internal medicine, and neurology. Since 2000, he has served on the faculty of Thomas Jefferson University, where he is currently a Professor of Neurology. Id. Since 2000, he has served as chief of the division of clinical neuroimmunology and the director of the Comprehensive MS Center. Id. He has authored numerous medical articles, belongs to several editorial boards and professional organizations, and has received numerous honors in his field. He testified that approximately 70 percent of his job involves direct patient care. Tr. 111. He sees patients across the neurological spectrum, but focuses on inflammatory diseases of the central nervous system, the most common of which is MS. Tr. 111-12. Dr. Leist's research is also focused on MS. Tr. 113. The undersigned accepted Dr. Leist as an expert in neurology. Tr. 114.

V. Analysis

1. Loving Prong One: Petitioner's condition before receiving the flu vaccine.

As detailed in the facts section above, petitioner appeared to be largely healthy before receiving the vaccine. The parties' experts, Dr. Steinman and Dr. Leist, agree that some of the non-enhancing lesions first detected on MRIs after the vaccine were probably present before the vaccine. Dr. Steinman explained that some factors, such as stronger MRI magnets or different doses of gadolinium, may affect the ability to see lesions or enhancement, but, in general, doctors look at enhancing lesions as new and ones that do not enhance as older or of indeterminate age. Tr. 10, 56.

Dr. Leist noted that in June 2012, petitioner had a one-week history of pain in her left shoulder, radiating to her arm, wrist, and hand. He contended that this could have been an early symptom of MS and it could be attributed to the non-enhancing lesion at C3-C4 detected by a December 1, 2013, cervical spine MRI. However, the primary care provider did not suspect MS. Following rest and prescription of a corticosteroid, these symptoms went away within a few days.

Otherwise, petitioner did not display any symptoms and she appeared quite healthy. She was an active mother of three children. She had partnered with her husband in running two restaurants. Shortly before receiving the vaccine, she had obtained her real estate license and planned to begin that new career. She reported feeling quite well upon receiving the flu vaccine on November 20, 2013. Indeed, the parties stipulate that she had no symptoms of MS at that time. Joint Prehearing Submission at ¶ 5.

2. Loving Prong Two: Petitioner's condition after receiving the vaccine.

Based on my review of the medical records set forth above, there is very little question that petitioner developed new signs and symptoms of MS beginning less than two days after the flu vaccine. Her initial symptoms were numbness and tingling in her feet, which then ascended through her legs and torso, almost up to her clavicles.

The initial two MRIs performed on November 25 and 26, 2013, less than one week after the vaccination, establish a baseline. The initial brain MRI showed one enhancing lesion, in the subcortical white matter of the parietal lobe, which was read as consistent with active demyelination. The initial brain MRI also showed seven non-enhancing lesions. Three of these were in the temporal lobes and at least two were radiating away from the lateral ventricles with a Dawson's finger appearance. Pet. Ex. 5 at 162; see also Pet. Ex. 63 (original images from this and the other MRIs).

The initial thoracic spine MRI showed one additional enhancing lesion, this one on the cervical spine. More specifically, it was a T2 hyperintense lesion within the central slightly posterior cord centered at the level of C7 which measured 4 x 4 mm transverse and 6 mm craniocaudal (in length). Pet. Ex. 5 at 164-65.

Compared to the initial brain MRI performed on November 25, 2013, the second brain MRI performed on February 12, 2014, showed significant progression. One existing lesion in the periventricular white matter lateral to the temporal horn of the left lateral ventricle, "previously 0.7 x 0.3 cm," had grown to "3.2 x 2.4 x 1.8 cm." There were two somewhat large new lesions, one in the left temporal lobe measuring up to 3.3 cm and another in the left parietal and deep white matter measuring up to 1.5 cm. There were a total of 15-20 lesions, of which seven were enhancing. Pet. Ex. 5 at 170; compare Pet. Ex. 5 at 162 (November 25, 2013 brain MRI showing eight lesions, of which only one was enhancing).

As petitioner's lesion burden increased, her symptoms also worsened. She developed worsened spastic and hemiparetic gait; a blind spot in the right upper quadrant of her vision; nystagmus; numbness in her leg; and a new Lhermitte's sign. She also developed problems with swallowing; balance; memory; fatigue; and concentration. Pet. Ex. 8 at 6-7.

Today, petitioner is very dependent upon her 81-year-old grandmother to operate her household and has not been able to be employed. She suffers from gait and cognitive dysfunction as well as extreme fatigue after relatively minor exertion. There is no dispute that she is currently suffering symptoms and impairments caused by MS.

3. Loving Prong Three: Petitioner's change in condition constitutes a significant aggravation.

As provided above, the Vaccine Act defines a significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). In the present case, petitioner has certainly met this definition. The parties agree that before she received the flu vaccine, she very likely had lesions in the brain and spine. She experienced one transient episode of left shoulder pain, which might possibly have been a symptom of MS, 17 months before receiving the flu vaccine. However, the differential diagnosis for this shoulder pain is large and contains many common conditions. It could include MS, but that diagnosis is quite speculative in light of the history. Regardless, petitioner had no other symptoms and was very healthy upon getting the vaccine. After getting the vaccine, she progressively developed numerous new lesions and significant new symptoms over the ensuing days, weeks and months.

The increase in lesions seen in the February 2014 MRI correlated with worsening symptoms from November 2013 – February 2014. The increased symptoms and lesions represent a very substantial worsening of her condition, constituting a "significant aggravation." The cause of that worsening will be addressed below, under Loving prong five.

4. Loving Prong Four (Althen Prong One): Petitioner has established a reliable and reputable theory of how the flu vaccine can cause the significant aggravation of MS.

Under Althen Prong One, petitioner must set forth a medical theory explaining how the vaccine could have caused her significant aggravation. Andreu, 569 F.3d 1367, 1375 (Fed. Cir. 2009); Pafford, 451 F.3d at 1355-56. This prong requires petitioner to make an evidentiary showing that the vaccine "can" cause the injury alleged. *Id.* at 1356.

Petitioner's expert Dr. Steinman opined that there is homology between components of the 2013 Fluvirin vaccine (received by petitioner) and components of myelin in the human body. He presented a theory of molecular mimicry, which explains how the introduction of the flu vaccine can cause an autoimmune response against myelin, which can cause significant aggravation of MS.

Dr. Steinman's theory was partly based on his review of the available medical literature. He opined that the most relevant study was by Markovic-Plese, who found that cloned human T-cells that reacted to an influenza virus hemagluttinin ("Flu-HA") peptide also reacted to three peptides derived from human myelin proteins (two proteins from myelin oligodendrocyte glycoprotein ("MOG") and one protein from 23-cycle nucleotide 3/ phosphodiesterase ("CNPase").[13] Markovic-Plese also found significant homology between Flu-HA and those myelin proteins. Dr. Steinman noted that Markovic-Plese's research was on T-cells and myelin proteins derived from a human subject diagnosed with MS. He believed that the study should be given significant weight for this reason, and that it supported the theory of the flu vaccine prompting an autoimmune response causing or contributing to MS.[14] Pet. Ex. 9 at 9; Tr. 27-28.

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[13] Markovic-Plese S., *High Level of Cross-Reactivity in Influenza Virus Hemagglutinin-Specific CD4+ T-Cell Response: Implications for the Initiation of Autoimmune Response in* Multiple Sclerosis, 169 J. Immun. 31 (2005) [Pet. Ex. 21].

[14] Dr. Steinman found the Markovic-Plese study to be most relevant to petitioner's case. He provided numerous other articles to support his explanation of molecular mimicry and how it can cause or significantly aggravate MS. I have fully reviewed these articles and agree that they support Dr. Steinman's opinion, but will not discuss them in detail. *See also* Wucherpfennig KW et al., *Recognition of the Immunodominant Myelin Basic Protein Peptide by Autoantibodies and HLA-DR2 Restricted T Cell Clones from Multiple Sclerosis Patients: Identity of Key Contact Residues in the B-Cell and T-Cell Epitopes*, 100 J. Clinical Investigation 1114 (1997) [Pet. Ex. 13]; Steinman L., *Autoimmune Disease*, 269 Scientific American 106 (1993) [Pet. Ex. 16]; Steinman L and Oldstone MBA, *More Mayhem from Molecular Mimics*, 3 Nature Medicine 1321 (1997) [Pet. Ex. 17]; Steinman L., *Immunology of Relapse and Remission in Multiple Sclerosis*, 32 Ann. Rev. Immunol. 257 (2014) [Pet. Ex. 18]; Bach JF, *The Effect of Infections on Susceptibility to Autoimmune Diseases*, 347 N. Engl. J. Med. 911 (2002) [Pet. Ex. 19]; Wucherpfennig KW and Strominger JL, *Molecular Mimicry in T-Cell Mediated Autoimmunity: Viral Peptides Activate Human T-Cell Clones Specific for Myelin Basic Protein*, 10 Cell 10 695 (1995) [Pet. Ex. 20]; Gautam AM et al., *A Polyalanine Peptide with only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis*, 176 J. Exp. Med. 605 (1992) [Pet. Ex. 22]; Gautam AM et al., *A Viral Peptide with Limited*

Dr. Steinman opined that Markovic-Plese's findings could be extrapolated to petitioner's case. Markovic-Plese's research involved a Flu-HA peptide sequence, YVKQNTLKL. Pet. Ex. 21 at 3. Dr. Steinman reported that mass spectroscopy of the 2013-14 Fluvirin vaccine petitioner received had the identical nine amino acid sequence, suggesting that the Fluvirin vaccine can cause the same cross-reactivity to myelin. Pet. Ex. 9 at 10.

He said that the dominant epitope that he studied in MS patients has been the myelin basic protein epitope between residues 83 and 99, and that often appears in his reports because he and his research them have studied it and found antibodies in the brains of MS patients. Tr. 27. He said that by 2015, he and his research team had actually studied Fluvirin, not for the purposes of this case, but for the understanding of another issue with molecular mimicry, so they had a huge database of what is actually in the vaccine. Tr. 28.

Dr. Steinman asserted that his and Markovic-Plese's findings of cross-reactivity were with the "dominant" epitope on myelin protein. He explained that the immune system tends to mount a stronger response against a dominant epitope. That immune response may spread and attack other components of the protein. Tr. 27-28.

Thus, Dr. Steinman concluded that there is sufficient cross-reactivity between the influenza vaccine administered to petitioner and the myelin components which are damaged in MS. He said that he would be quite comfortable presenting this theory at grand rounds at a university hospital. Tr. 35.

Dr. Leist challenged this theory because Markovic-Plese's findings were from just one MS patient (which Dr. Steinman acknowledged). Dr. Leist also cited to an Institute of Medicine ("IOM") committee report for the proposition that epidemiological studies have not demonstrated an increased risk for MS after vaccination. [15] Dr. Leist also stated that he provides vaccinations to all of his patients with MS.

I have fully considered all of the opinions and medical literature submitted. Molecular mimicry has been accepted as a theory of causation in numerous vaccine cases. Dr. Steinman has done considerable research in the field of molecular mimicry, particularly as it relates to myelin and the causation of MS. He has demonstrated homologies between three different components of myelin and the influenza vaccine, and in particular the one administered in this case.

While Dr. Leist is correct that epidemiology has not demonstrated a statistically significant increase in MS cases after vaccination, it is well recognized that epidemiology is not particularly effective in identifying rare events and thus is not required to establish any Althen prong. Grant, 956 F.2d at 1149; Andreu, 569 F.3d at 1380. For these reasons, Dr. Leist's citation to the Institute of Medicine committee report is not persuasive. That committee could

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Homology to a Self-Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis, 161 J. Immunology 60 (1998) [Pet. Ex. 23].

[15] Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality, 318-21 (Stratton et al., eds. 2012) [Resp. Ex. F].

not assess the association between flu vaccine and relapse of MS in adults because the two epidemiological studies available "lacked validity and precision." Resp. Ex. F at 3. The committee concluded that the evidence was "inadequate to accept or reject a causal relationship" between flu vaccine and MS relapse. Id. at 5.

Both doctors advocate vaccination for their MS patients and advocate for vaccination in general. But Dr. Steinman has demonstrated a theory that is sufficient to explain how the vaccine could cause an aggravation of an asymptomatic or radiologically isolated MS, and I have concluded that his theory has satisfied Althen Prong One.

5. Loving Prong Five (Althen Prong Two): Petitioner has established a logical sequence of cause and effect between the flu vaccine and her significant aggravation.

Above, under Loving Prong Three, I concluded that petitioner suffered a significant aggravation of her prior condition. Under Loving Prong Four (Althen Prong One), I concluded that the Fluvirin vaccine could cause an aggravation of a previously asymptomatic MS through the mechanism of molecular mimicry. Under Loving Prong Five (Althen Prong Two), the question is whether petitioner has shown a logical sequence of cause and effect between the flu vaccine and her significant aggravation. In other words, would petitioner's condition have progressed the way that it did "but for" the introduction of the vaccine? Hennessey, 2009 WL 1709053, at *58 (citing Shyface, 165 F.3d at 1352).

Dr. Steinman opined that flu vaccine more likely than not triggered a substantial aggravation of a formerly asymptomatic, radiologically isolated MS which he believed could have remained asymptomatic indefinitely but for receipt of the vaccine.

Dr. Leist disagreed, opining that petitioner's MS was already symptomatic. The only specific symptom he identified was her shoulder pain and numbness in June 2012. He opined that this was more than likely a clinical symptom of MS and it could be attributed to the C3-C4 lesion that was non-enhancing on the December 1, 2014, MRI. He further testified that it is not unusual for an individual to have symptoms of MS before he or she is ultimately diagnosed. Tr. 120-123.

On cross-examination, Dr. Steinman conceded that he could not exclude the possibility that these shoulder symptoms could have been clinical symptoms of MS. Tr. 54. He also agreed that non-enhancing lesions were of indeterminate age, so they may have existed before the vaccine. Tr. 57. However, shoulder pain is quite ubiquitous and has many common causes. The treating doctor at the time did not consider that it could be anything but a garden-variety issue, which indeed did go away several days later. Dr. Leist is correct that MS symptoms can appear at remote times and are not recognized in isolation as a part of an MS diagnosis, which frequently is not made until much later. But it is entirely too speculative to conclude that this single event was a manifestation of MS, particularly when there were no other symptoms whatsoever in the intervening 17 months.

Beyond the shoulder symptoms, the experts disagreed further about petitioner's expected course but for the vaccine. Dr. Steinman opined that MS can be latent (asymptomatic) and only apparent radiologically. Pet. Ex. 30 at 1. He cited the Okuda study for the proposition that some patients can have "radiologic MS" and never have any disabilities.[16] That study followed 451 patients that were initially identified to have "MS-like" lesions. Only 34% of those patients developed clinical MS over the course of five years. Dr. Steinman opined that petitioner could have been one of the patients to never develop any clinical symptoms.

Dr. Steinman also stated that a patient's clinical condition often correlates to the number and size of lesions. He noted that while petitioner did have lesions that probably predated the vaccine, after the vaccine, she suffered a remarkable increase in both the number and the size of lesions in the subsequent months. As I have observed above under Loving Prong Two, these radiologic changes were accompanied by new symptoms. Pet. Ex. 30 at 1.

Dr. Steinman also opined there is no "typical course of MS" and the course of petitioner's previously asymptomatic MS absent the vaccine could not be definitively predicted. However, he opined it was more likely than not that the vaccine was responsible for the significant increase in lesions and onset of symptoms based on his theory and on his review of petitioner's records. Pet. Ex. 30 at 1-2.

Dr. Leist responded that even if petitioner's shoulder pain and numbness are not found to be clinical signs of MS prior to vaccination, based on the lesions found on her MRI, petitioner had a high risk of converting to a clinical form of MS. Tr. 128-30. He pointed to the Okuda article, Table 4, which provides that subjects with spinal cord involvement have a significantly higher probability of experiencing a first clinical event. Tr. 133 (citing Pet. Ex. 67 at 7). Dr. Leist stated that petitioner was at this higher risk because of the small non-enhancing C3-C4 lesion observed five days after the vaccination. Tr. 133-35. Dr. Steinman conceded that petitioner's C3-C4 lesion may have been present before the vaccination. He noted that the Okuda study showed that patients with spinal cord involvement had an increased risk, but not a guarantee of experiencing a clinical event. In fact, after five years, approximately 50% of patients with spinal cord involvement were still asymptomatic. Tr. 187-88 (citing Pet. Ex. 67 at 6).

Dr. Leist also contended that petitioner had symptoms of a viral illness around the time of her significant aggravation, which would be a more likely cause of the same. He cited a study by Correale which showed an increase in MS relapse after documented infections. Dr. Leist's characterization of this article is accurate. [17]

However, the medical records and testimony in this case do not establish that petitioner had an infection. The triage note from November 23, 2013 (five days after the vaccine) provides that petitioner "has not had a fever recently but does endorse recent runny nose." Pet. Ex. 5 at

[16] Okuda DT et al., *Radiological Isolated Syndrome: 5-Year Risk for an Initial Clinical Event*, 9 Plos One e90509 (2014) [Pet. Ex. 67].

[17] Correale et al., *The Risk of Relapses in Multiple Sclerosis During Systemic Infections*, 67 Neurology 652 (2006) [Resp. Ex. C].

21. However, none of the other many histories or physical exams mentions a runny nose. Upon testifying at the hearing, petitioner denied any memory of having a runny nose. Tr. 105. While certain of her children did develop fevers after receiving their vaccines, there is no indication that petitioner did at any time. Pet. Ex. 5 at 17. The emergency room records (which contain the one mention of a runny nose) also document a physical exam and lab work, which did not reveal a viral infection or mention a runny nose. Pet. Ex. 5 at 17, 26, 29. As Dr. Steinman noted, petitioner was then thoroughly evaluated and tested at the University of Utah Hospital, where no mention was made of a runny nose or viral illness and numerous temperatures were normal with no fever. Additionally, blood work looking for many different viral and bacterial antigens tested negative. Dr. Steinman did agree that there was an association between illness and MS relapse. Tr. 60. However, he noted that there was no evidence that there was an infection present much less what specific virus or bacterium might have been active. He further noted that a very thorough evaluation was done by medical professionals at the University of Utah, who did not see any evidence of infection. Tr. 48.

While respondent contends that the existence of a viral illness informs whether or not there is a logical sequence of cause and effect between the flu vaccine and petitioner's injury, respondent also suggests that a viral illness would be a more likely cause of petitioner's MS "relapse." It is respondent's burden to establish by a preponderance of the evidence that petitioner's injury was caused by a factor unrelated to the vaccine. A factor unrelated cannot be "any idiopathic, unexplained, unknown, hypothetical, or undocumented causal factor, injury, illness, or condition." Knudsen, 35 F.3d at 548; § 13(a)(1)(B). In this case, I agree that a viral illness cannot be ruled out, but respondent has not shown that it was present based on the available evidence. In fact, the physical exams and extensive lab work tend to show the opposite, that petitioner did not have an infection at the time of the onset of her MS symptoms. Her doctors at the University of Utah observed that she had suffered no prior symptoms to account for her non-enhancing lesions and that she did not appear acutely ill with an infection making a viral infection "less likely" as an explanation for her symptoms than her influenza vaccination. Joint Prehearing Submission, ¶ 22.

After full consideration of the evidence, I find that petitioner and her expert Dr. Steinman have established a logical sequence of cause and effect between the flu vaccination and the significant aggravation of her MS. As noted above, I find it more likely than not that before the flu vaccination, petitioner's MS was latent and that her June 2012 shoulder pain was not a manifestation of MS. Dr. Steinman has persuasively opined, based on the Okuda article, that MS can remain latent for many years. The Okuda article showed that spinal cord involvement was associated with an increased risk, but not a guarantee, of a first clinical event. The course of the disease after the onset, in this previously asymptomatic woman, is strongly suggestive of the vaccine as a trigger of the substantial aggravation of her previously asymptomatic disease as both the symptoms and lesion burden increased significantly between the day of the vaccination and the February 2014 MRI. Given the presence of non-enhancing lesions together with enhancing ones shortly after the vaccination, my Althen prong two analysis is substantially interwoven with the Althen prong three analysis which will be addressed directly below.

6. Loving Prong Six (Althen Prong Three): Petitioner has established a medically acceptable temporal relationship between the flu vaccination and her significant aggravation.

Under Loving Prong Six (Althen Prong Three), petitioner must establish a "medically acceptable temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281.

In this case, both parties and their experts devoted significant attention to the timing of petitioner's symptoms and whether an immune response could have caused the onset of her symptoms approximately 40-41 hours after the flu vaccination. Dr. Steinman opined that it could, particularly when the response was a recall response to an antigen previously seen by the immune system in previous vaccines as was the case here. Pet. Ex. 9 at 12-13; Pet. Ex. 46 at 1-2.

In his first report, Dr. Steinman cited studies by Schonberger and Langmuir for the proposition that the swine flu vaccine had been associated with the onset of Guillain-Barré Syndrome ("GBS") within as little as 0 to 1 days. Pet. Ex. 9 at 12.[18] He allowed that the temporal association between the swine flu vaccine and the onset of GBS cannot necessarily be used as an "absolute surrogate" for the temporal association between the flu vaccine received by petitioner and the onset of clinical MS. Id. Respondent and Dr. Leist contended that these studies were not applicable. They emphasized that GBS is a disease of the peripheral nervous system, while MS is a disease of the central nervous system. See, e.g., Resp. Post-Hearing Brief at 6. However, Dr. Steinman also cited multiple case studies of central nervous system conditions manifesting within one to two days after flu vaccinations. Pet. Ex. 9 at 13[19]; Pet. Ex. 46 at 2.[20]

Dr. Steinman also cited a study by Bartholomäus for the proposition that activated immune cells gain access to the brain and spinal cord within 1 day.[21] Pet. Ex. 9 at 11, 13; Pet. Ex. 46 at 2. He stated that Bartholomäus took T-cells previously exposed to myelin basic protein and injected them into mice. The first T-cells "appeared in the CNS… on days 1-2.5 after transfer." The mice then developed paralysis – a clinical sign of experimental autoimmune encephalomyelitis ("EAE") - after approximately three days. Pet. Ex. 46 at 13. Dr. Steinman stated that because the T-cells were previously exposed to myelin basic protein, upon injection,

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[18] Schonberger LB et al., *Guillain-Barré Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-77*, 110 Am. J. Epidemiol. 105 (1979) [Pet. Ex. 24]; Langmuir AD et al., *An Epidemiologic and Clinical Evaluation of Guillain-Barré Syndrome Reported in Association with the Administration of Swine Influenza Vaccines*, 119 Am. J. Epidemiol. 841 (1984) [Pet. Ex. 25].

[19] Rabello GD, *Post-Vaccinal Neurological Complications*, 71 Arq. Neuropsiquiatr. 747 (2013) [Pet. Ex. 26].

[20] Wu Y et al., *Reversible Post-Vaccination Paraneoplastic Encephalomyelitis in a Patient with Lung Adenocarcinoma*, 120 Int. J. Neuroscience 792 (2010) [Pet. Ex. 52]; Sacheli A and Bauer R, *Influenza Vaccine-Induced CNS Demyelination in a 50-Year-Old Male*, 15 Am. J. Case Rep. 368 (2014) [Pet. Ex. 53]; Larner AH and Farmer SF, *Myelopathy Following Influenza Vaccination in Inflammatory CNS Disorder Treated with Chronic Immunosuppression*, 7 E. J. Neurology 731 (2000) [Pet. Ex. 54].

[21] Bartholomäus I et al., *Effector T Cell Interactions with Meningeal Vascular Structures in Nascent Autoimmune CNS Lesions*, 462 Nature 94 (2009) [Pet. Ex. 48]; Supplemental Figures from Bartholomäus et al., Nature [Pet. Ex. 49].

they mounted a recall response reflected by the presence of T-cells in the CNS. Tr. 13. In response, Dr. Leist discounted the significance of T-cells in the CNS, opining that they "may not lead to clinical symptoms." Dr. Leist also opined that the recall response against the myelin basic protein resulting in paralysis after three days did not support the timing in this case. Tr. 159. Upon consideration, the Bartholomäus study does provide some support for Dr. Steinman's timing of a recall response reaching the CNS. Dr. Leist did not explain why this would not lead to clinical symptoms. Additionally, while the timing reported by Bartholomäus is slightly longer, it is comparable to the two-day period in petitioner's case. This is especially true because Bartholomäus, studying mice, recorded only those symptoms that were outwardly observable (flaccid tail; gait disturbance; paralysis; and death), whereas petitioner initially reported only sensory symptoms - numbness and tingling in her feet, which later affected her gait.

Dr. Leist also suggested that the timing would be longer, based on a study by Rowhani-Rahbar, who reported that the "biologically plausible" timing between flu vaccination and acute disseminated encephalomyelitis (ADEM) would be 2-42 days.[22] Tr. 159-60. However, this article is about the initial onset of ADEM, which is a monophasic CNS condition. It does not involve a recall response. This does not conflict with Dr. Steinman's opinion that a subject who already had been exposed to a vaccine antigen would mount a more rapid recall response. Tr. 40; Tr. 134, 174. Moreover, petitioner's onset within 40-41 hours is just outside the 2-42 day time frame proposed by Rowhani-Rahbar.

Most importantly, Dr. Steinman opined that a rapid response would be medically-acceptable and indeed likely in a recall situation. He explained that vaccinations are given to create adaptive memory responses to the antigen contained in the vaccine so that the immune system will respond rapidly and robustly to an exposure to the wild antigen at some time in the future and thus prevent disease. Dr. Steinman cited an IOM publication to explain that the immune response has a lag phase, a logarithmic phase, and finally a plateau.[23] Pet. Ex. 46 at 1. The IOM provides: "The lag phase is characterized by the initial activation of the B and T cells upon encounter with the antigen for which they are specific." Pet. Ex. 47 at 58. The lag phase between initial exposure to the antigen and the logarithmic phase is classically thought to be four-to-seven days, but it varies depending upon the route of exposure and the antigen itself. Id. Due to the development of memory B and T cells during the primary immune response, the latency between subsequent exposure to an antigen and the immune response is usually shorter. Id. In a recall response, "[t]he lag phase is generally 1 to 3 days; the logarithmic phase of the secondary antibody response occurs over the next 3 to 5 days." Id.

According to Dr. Steinman, the IOM publication shows that the immune system can "rev up for a recall response, and within a day, two days, it's really firing off, and then it goes into a logarithmic phase." Tr. 37. He characterized the logarithmic phase as going into "hyperdrive."

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[22] Rowhani-Rahbar A et al., *Biologically Plausible and Evidence-Based Risk Intervals in Immunization Safety Research*, 31 Vaccine 271 (2012) [Resp. Ex. H].

[23] Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality, Chapter 3: Evaluating Biological Mechanisms of Adverse Events, pp. 57-62, 70-73, 91-101 (Stratton et al., eds. 2012) [Pet. Ex. 47].

Tr. 38. He also noted that vaccines are designed to develop this recall response, which allows a faster, more effective response to viruses. Pet. Ex. 46 at 1; Tr. 36.

Dr. Steinman opined that it was likely that petitioner had a recall response because she had previously received flu vaccines in 2009 and 2011 before receiving the flu vaccine in November 2013 at issue in this case. Pet. Ex. 46 at 2 (citing Pet. Ex. 39 at 2; Pet. Ex. 2 at 9). Dr. Steinman stated that the 2009 and 2011 vaccines both contained the B/Brisbane/60/2008-like virus. The 2011 and 2013 vaccines both contained the A/California/7/2009-like virus. Dr. Steinman opined: "Thus, there is sufficient cross-reactivity between the various seasonal influenza vaccines that [petitioner] received. This makes a rapid recall response in 2013 even more likely." Pet. Ex. 46 at 2-3.[24]

Dr. Steinman explained: "The latency period between petitioner's exposure to the 2013 flu vaccine and the onset of symptoms of her demyelinating disorder (about 40 hours) thus fits the expected lag phase between subsequent exposure to an antigen and development of the immune response (at one-to-three days). At this point, the 'logarithmic phase' kicks in, and clear-cut pathology would be readily apparent once the immune system is 'revved up.'" Pet. Ex. 46 at 1.

Dr. Steinman opined that petitioner's symptoms were consistent with a recall response followed by a logarithmic response. The recall response was manifested less than two days after the vaccination when she developed numbness in her feet. The logarithmic phase occurred over the subsequent days, as the numbness and tingling rose up through her legs and through her torso, almost to her clavicles by the ninth day after the vaccination.

Dr. Steinman added that petitioner's initial symptoms could be attributed to the enhancing lesion seen on the brain MRI five days post-vaccination, and the enhancing C7 lesion seen both on the thoracic MRI six days post-vaccination and the spinal MRI 11 days post-vaccination. These enhancing lesions suggest that something was quite active in conjunction with her symptoms in this post-vaccinal period. Dr. Steinman believed these active lesions were further evidence of the flu vaccine triggering a recall response against myelin in her body. Tr. 49-50.

Another focus of the timing debate focused on the significance of the enhancing and non-enhancing lesions found on petitioner's MRIs, the first of which occurred five days after the flu vaccination. Dr. Steinman and Dr. Leist agreed that the enhancing lesions were new. A transient breakdown in the blood-brain barrier allowed the gadolinium contrast to come through and enter the central nervous system, thereby causing the enhancement at the sites of the lesions.

[24] FDA Press Release: Influenza Virus Vaccine for the 2009-2010 Season [Pet. Ex. 55]; FDA Press Release: Influenza Virus Vaccine for the 2011-2012 Season [Pet. Ex. 56]; FDA Press Release: Influenza Virus Vaccine for the 2013-2014 Season [Pet. Ex. 57].

Dr. Steinman said that it is not known whether all enhancing lesions are new. Dr. Leist submitted a study by Rocca[25] for the proposition that "changes at the site of future enhancing MS lesions can be detected six weeks before the start of enhancement." Resp. Ex. A at 5. Rocca performed MRIs on six subjects with MS each week for 12 weeks. Rocca utilized the MRIs and computer reconstruction for diffusion tensor imaging, which measures diffusivity (the movement of water) in the brain. Rocca found that the MS subjects displayed some changes in diffusivity before displaying enhancing lesions. Thus, Dr. Leist argued that enhancement is not the first sign of a new lesion. Tr. 122. Dr. Steinman noted that the Rocca study had only six patients, and had the most significant change in diffusivity on day zero before the enhancement was seen. Dr. Steinman did acknowledge that there were some changes seen earlier, as much as six weeks, but that the most common changes were seen at virtually the same time as the beginning of enhancement. Tr. 50-51.

In any event, Dr. Steinman and Dr. Leist agreed that in this case, it was likely that petitioner's MS was preexisting because the first MRIs showed multiple non-enhancing lesions. Both accepted the Cotton study[26] which found, based on weekly MRIs to MS patients, that the median period of enhancement was two weeks. Dr. Leist conceded that Cotton found that the majority of new lesions enhanced for only one to two weeks and the distribution of new lesions was skewed toward enhancement for one week or less. Tr. 171. Dr. Leist also acknowledged that small lesions would enhance for less time than large ones. Tr. 172.

In this case, the initial MRI ordered was a lumbar spine study because the first symptoms were limited to the lower extremities. These films served only to rule out lumbar spine pathology. On November 25, 2013 (five days post-vaccination), a brain MRI showed eight foci of T2 hyper-intensity, one of which enhanced. Joint Pre-Hearing Submission, ¶ 17. On November 26, 2013 (six days post-vaccination), a thoracic MRI showed a single hyper-intense lesion at C7 and no other abnormality. Id. at ¶ 18. Despite treatment with Solu-Medrol, petitioner's symptoms continued to get worse and the numbness had almost reached her clavicles by November 29, 2013. Id. at ¶ 20. The next day, petitioner and her grandmother drove to Salt Lake City to the University of Utah Medical Center. On December 1, 2013, (eleven days post-vaccination), a cervical spine MRI showed that the same C7 lesion was still enhancing. This film also demonstrated a small lesion at C3-C4 that was non-enhancing. Id. at ¶ 22.

The actual MRI films were filed only at the conclusion of the hearing and they were not reviewed by either Dr. Steinman or Dr. Leist. Thus, the experts did not opine as to whether the November 26, 2013, thoracic spine MRI would have shown the small C3-C4 lesion that was not enhancing when found later on December 1, 2013. However, it is unlikely, as the radiologist noted, that the thoracic spine MRI captured "the bottom of C4" down to L1. Pet. Ex. 5 at 164. It is possible that the C3-C4 lesion was present before the vaccination. It is also possible that after the vaccination, the C3-C4 lesion appeared, enhanced, and then stopped enhancing by the cervical spine MRI on December 1, 2013 (11 days after vaccination). This is quite plausible based on the Cotton study, which indicates that MS lesion enhancement is skewed towards a

[25] Rocca et al., *Weekly Diffusion-Weighted Imaging of Normal-Appearing White Matter in MS*, 55 Neurology 882 (2000) [Resp. Ex. E].

[26] Cotton et al., *MRI Contrast Uptake in New Lesions in Relapsing-Remitting MS Followed at Weekly Intervals*, 60 Neurology 640 (2003) [Resp. Ex. D].

time period of one week or less, and that small lesions tend to enhance for less time than larger ones

Dr. Steinman opined that the November 20, 2013, flu vaccination "most likely triggered" the "new" lesion in the subcortical white matter of the right parietal lobe, found to be enhancing on the November 25, 2013 brain MRI. Pet. Ex. 11 at 3. Dr. Leist contended that because Cotton showed that the "average lesion enhanced for about 2 weeks," it was "quite likely" that the right parietal lesion was present and enhancing before the flu vaccination. Resp. Ex. A at 5. This argument is difficult to resolve because it is not known how long the right parietal lesion continued to enhance. Petitioner did not undergo another brain MRI until February 2014. On this argument, I find that the evidence is at least in equipoise. It is plausible that the right parietal lesion developed in correlation with petitioner's symptoms after the flu vaccination.

Dr. Leist opined that the C7 lesion also was present before the vaccination. Resp. Ex. H at 2-3. There is less support for this assertion, as the C7 lesion was enhancing both on November 26, 2013 (six days post-vaccination) and on December 1, 2013 (eleven days post-vaccination). The timing of a significant aggravation following the flu vaccination is further supported by the later MRIs, which demonstrate growth of the existing lesions and the presence of new enhancing lesions.

Dr. Steinman argued that the relatively mild onset of symptoms on the second day after the flu vaccination, followed by a rapidly progressing set of symptoms and radiologic findings that by February 12, 2013, had increased to 15-20 brain lesions which were larger and seven of which were enhancing was consistent with an autoimmune cross reaction triggered by the vaccine leading to significant disease. As noted above, he supported the early onset with reference to multiple case studies of CNS symptoms within one to two days of a vaccination.

Dr. Leist contended that there was not a medically-acceptable period of time between petitioner's flu vaccination and the symptoms and signs of clinical MS.[27] Dr. Leist noted that on November 23, 2013 (three days after the flu vaccination), petitioner had an elevated IgG index of 0.71 and six oligoclonal bands. Resp. Ex. A at 2, 5 (citing Pet. Ex. 3 at 66; Pet. Ex. 4 at 16; Pet. Ex. 5.1 at 29-30; Pet. Ex. 5.2 at 34). Dr. Leist stated that both IgG index and oligoclonal bands

[27] Dr. Leist initially stated, consistent with Dr. Steinman, that onset was approximately two days after the vaccination when petitioner developed numbness and tingling in her feet. *See* Resp. Ex. H at 1. At the entitlement hearing, Dr. Leist suggested that onset was almost immediately after the vaccination, based on a December 1, 2013, record which provides: "On 11/30/13, [petitioner] had a flu vaccine . . . After the vaccine, she immediately felt a weird reaction in her chest." Pet. Ex. 7 at 16. This record contains a typo, as the vaccination was actually given on November 20, 2013. The second relevant record is from December 31, 2013, when Dr. Steffens wrote that petitioner "had received a flu vaccine and felt immediately a weird sensation in her chest. Two days later, she began noticing paresthesias, pins and needles, in her feet." Pet. Ex. 8 at 2. Dr. Leist suggested this "may have represented an MS hug" attributed to the C7 lesion which was seen to be enhancing six days after the vaccination. Tr. 125. There is insufficient evidence to suggest this was the onset of petitioner's injury. First, the majority of the medical records (including several records that were earlier in time) provide that onset was the numbness and tingling in her feet. See, e.g., Pet. Ex. 3 at 13; Pet. Ex. 5.1 at 16, 20; Joint Pre-Hearing Submission at 3. Second, petitioner testified that she did not recall feeling a weird sensation in her chest after the 2013 flu vaccination at issue. She may have been referring to a sensation in her chest after the first flu vaccination in 2009. Tr. 107-08. I find that the majority of records and petitioner's recollections are more likely to be accurate than the two records cited by Dr. Leist.

serve as evidence of a longer-standing inflammatory process in the central nervous system. Resp. Ex. A at 5. Dr. Leist opined it was "inconceivable" that the flu vaccine caused these to develop within three days. Thus, the elevated IgG index and oligoclonal bands were "biologic proof of inflammatory activity in the central nervous system" that began before the flu vaccination. Resp. Ex. G at 1. He challenged Dr. Steinman to provide medical literature showing that these could develop within such a short period of time. Tr. 134-37. Therefore, Dr. Leist opined that something else prior to the vaccine had prompted the elevated IgG index and oligoclonal bands. He noted that Okuda listed these abnormal CSF findings as another risk factor for developing clinical MS. Tr. (citing Pet. Ex. 67 at 7). Dr. Steinman responded that the oligoclonal bands could develop within three days of the vaccination, as part of the recall response discussed above. He stated that oligoclonal bands are made up of immunoglobulins which are non-specific. They may already have been in the body from petitioner's earlier flu vaccinations and/ or other infections. Once the November 2013 flu vaccination was given, they would have mounted a recall response. Tr. 39-41. In this case, neither expert submitted literature specifically about the timing of these CSF results. I find that Dr. Steinman's general explanation of a recall response is applicable to the CSF findings and is more persuasive in this case.

While the rapid onset of petitioner's symptoms is somewhat unusual, the fact of the likelihood of a recall response to a strain of the flu vaccine which petitioner had received before provides a reasonable and logical explanation. I have concluded that the timing of the onset of symptoms and the increase in lesion burden was consistent with Dr. Steinman's explanation of the mechanism of a recall response. The progression of the lesion burden and symptoms in the three months following the onset of the early sensory symptoms reinforced the conclusion that the vaccine triggered the onset of symptomatic MS in a previously asymptomatic patient. Dr. Steinman's explanation of the timing and his supporting literature are also persuasive. Accordingly, I have concluded that petitioner has established Loving prongs five and six (Althen prongs two and three).

VI. Conclusion

After a review of the entire record and for the foregoing reasons, I have concluded that petitioner has established that the covered flu vaccination more likely than not caused-in-fact the significant aggravation of her multiple sclerosis. She is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master